DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

95176d

JAN 27 2005

WARNING LETTER

VIA FEDERAL EXPRESS

John W. Marcum, M.D.
Childrens Hospital Los Angeles
4650 Sunset Boulevard
Los Angeles, California 90027

Dear Dr. Marcum:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection conducted at your clinical site. This letter also discusses your written response, dated October 25, 2004, to the noted violations and requests that you implement prompt corrective actions. Ms. Diane C. Van Leeuwen and Ms. Kirtida Patel, investigators from FDA's Los Angeles District Office, conducted the inspection from September 8 through September 23, 2004.

The purpose of the inspection was to determine if your activities as a clinical investigator for the [redacted] study complied with applicable FDA regulations. The [redacted] is a device as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. 321(h)] because it is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, or because it is intended to affect the structure or any function of the body.

FDA conducted the inspection under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification [510(k)] submissions are scientifically valid and accurate. The program also ensures that human subjects are protected from undue hazard or risk during scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 – Investigational Device Exemptions, 21 CFR Part 50 – Protection of Human Subjects, and Section 520(g) of the Act. At the close of the inspection, Ms. Van Leeuwen and Ms. Patel presented a Form FDA 483 "Inspectional Observations" to you for review and discussed the listed deviations. Dr. David Moromisato, Co-Investigator, and [redacted] were also present. The deviations noted on the FDA 483, your written response, and our subsequent inspection report review are discussed below:

Failure to conduct the investigation in accordance with the investigational plan and to control devices under investigation (21 CFR 812.100, 812.110(b)).

Pursuant to 21 CFR 812.100 and 812.110(b), clinical investigators are required to ensure that investigations are conducted according to the signed agreement, the Investigational Plan, and applicable FDA regulations, as well as any conditions of approval imposed by the IRB or FDA. The study protocol is part of the Investigational Plan (21 CFR 812.25(b)). Examples of your failure to comply with these requirements include, but are not limited to, the following:

- Your investigational plan/protocol required that prompt reporting be made of significant adverse events to the IRB in writing within five days of occurrence and within 24 hours of serious adverse events. There were nine subjects in your study who developed infections, which were not reported to the IRB within five days. There were also four deaths during the study period, which were not reported to the IRB within 24 hours.

- Specific measurements were to be collected from routine patient care data during the study period and transcribed onto Case Report Forms, of which the following were not collected: [redacted] Primary outcomes were required to be analyzed for [redacted], but were not recorded or analyzed. Secondary outcomes which were required to be analyzed such a[redacted] were not recorded or analyzed.

- Fifty subjects were required to achieve[redacted] however, the investigator terminated the study after 32 subjects completed the study because the investigator felt the amount of data was sufficient.

  In your response you state that you have notified, or are taking steps to notify, the IRB of the infections, deaths, adverse events, protocol changes, and deviations. You stated that you will also manually enter all data onto your Case Report Forms and that you have filed a change of status form to the IRB from enrollment to data collection and analysis. We find your responses acceptable.

- The devices under investigation were not properly controlled, in that test articles were stored in various offices and the investigators did not always have knowledge of exactly when the test articles were removed after[redacted]

devices. Therefore, there was no assurance that non-research physicians, fellows or any other staff did not have access to the devices. In addition, the devices were not labeled as investigational, as required by 21 CFR 812.5.

In your response, you state that for further studies, you will ensure that devices are properly controlled by utilizing an office with a cabinet accessible only by the investigators. We find your response acceptable.

Failure to prepare and submit to the sponsor and the reviewing IRB a complete, accurate, and timely report of an unanticipated adverse device effect no later than 10 working days after first learning of the effect (21 CFR 812.150(a)(1)).

A complete, accurate, and timely report of an unanticipated adverse device effect was not prepared and submitted within 10 working days after first learning of the effect, to the sponsor and the reviewing IRB, as required by 21 CFR 812.150(a)(1). Furthermore, the IRB procedures and study protocol required that reporting of Serious Adverse Events (SAEs) that result in death while the subject is enrolled in the study or within 30 days of the completion of the study be reported to the IRB within 24 hours of knowledge of occurrence. You failed to report the deaths of four subjects to the IRB. The IRB procedures and study protocol also required that all other serious unexpected events, including hospitalizations, involving risks to subjects or others that are judged "possibly related" or "related" be reported to the IRB within five days of knowledge of occurrence. Nine such events occurred that were not reported to the IRB within 10 days of the investigator's knowledge of the occurrence.

As discussed above, this issue was addressed in your response. You also submitted an outline to your IRB with rates of expected serious adverse events in your patient population; we find these responses acceptable.

Failure to maintain accurate, complete, and current records relating to the investigator's participation in an investigation (21 CFR 812.140(a)).

FDA regulations require investigators to maintain accurate, complete, and current records relating to the investigator's participation in an investigation (21 CFR 812.140(a)). Examples of study data inaccuracies and inconsistencies observed in your study records include, but are not limited to, the following:

- Records of receipt, use, and disposal of the device that relate to the type and quantity, dates of receipt, and batch number or code mark are not all complete. You had no records to indicate the date, the amount, or lot number of devices received. There were no records indicating the number of devices used or the lot numbers used on each subject. There were no records of the date, amount and lot numbers of devices returned. You state in your response that you will now track this data. This is an acceptable response.

- Records showing dates and reasons for each deviation from the protocol are not all complete. You state in your response that in the future, you will notify the IRB and carefully document your rationale for any deviation in the study, which we find to be an acceptable response.

Records relating to correspondence with the IRB and sponsor, including required reports, are not all complete. For instance, there is no correspondence demonstrating that the sponsor and IRB were notified of all adverse events and serious adverse events, including the nine infections and four deaths. The sponsor and IRB were not notified of the decision to deviate from or modify the approved protocol. For example, the data was not collected per protocol and the number of subjects was modified. It was also noted in the inspection report that the actual protocol version used for the conduct of the study (dated 10/02/03) was the version that was last submitted and not the version approved and returned by the IRB. This version was an electronic copy maintained in the computer and was not printed, copied and distributed to all participating clinical investigators. In your response, you have stated that the sponsor and IRB will be notified and correspondence documented; we find these responses acceptable.

- Records for each subject concerning anticipated and unanticipated adverse device effects are not all accurate, complete, and current. A record of each subject's adverse device effect was not maintained. Anticipated events were identified in the protocol as minimal; however, they were not specifically listed in the Informed Consent Form or the protocol. In addition, the unanticipated events, such as the nine infections discussed above, were not fully recorded by the investigator for each of the affected subjects. In your response, you state that you will maintain a record of subject adverse events and inform patients of all foreseeable risk prior to entry into studies. We find these responses acceptable.

- Records of each subject's exposure to the device, including the date and time of each use and the use of any other therapy, are not all complete. As required by the protocol, the device was to be administered to the subject at [redacted] and [redacted] after the subject was [redacted] The times and length of the exposure to the device were not reported on the Case Report Forms. The investigator stated that the duration of the exposure of the device could range from [redacted] He stated that the exposure to the device normally occurred at the same instance as [redacted] These times had to be interpreted on the [redacted] however, the times listed in these reports were not collection times but rather the time the samples were run in the laboratory; therefore, it remains unclear when or for how long the devices were exposed during each interval. You state in your response that in future studies, the exact time and length of exposure for each device will be recorded for each patient; we find your response acceptable.

- Records of each subject's case history are not all accurate. Specifically, several Case Report Forms had data times and results which did not match raw data time and results, particularly for the [redacted] The FDA investigators noted the Case Report Forms in general were incomplete with various cross-outs and changes by multiple authors, and an occasional white-out. In addition, one informed consent form was noted to be missing [redacted] In your response you included a copy of corrected data records and you state that system problems with the computerized medical record are being addressed, that copies of all raw data will be made and/or attached to the Case Report Form, and that a time range will be provided if there will is a variation in the timing of data collection. We find these responses acceptable.

You state that you are working closely with the IRB to insure that any future studies you may be allowed to perform are consistent with the Good Clinical Practices guidelines. **FDA may verify the adequacy of these corrections during a future inspection.**

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a clinical investigator to assure adherence to each requirement of the Act and all applicable federal regulations.

Within 15 working days after receiving this letter, please provide written documentation of any additional, specific steps you have taken or will take to correct these violations and prevent the recurrence of similar violations in current and future studies. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 CFR 812.119. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch, HFZ-312, 2094 Gaither Road, Rockville, Maryland 20850, Attention: Viola Sellman.

We are also sending a copy of this letter to FDA's Los Angeles District Office, 19701 Fairchild, Irvine, California 92612. We request that you also send a copy of your response to that office.

If you have any questions, please contact Ms. Sellman by phone at 240-276-0125, or by email at vxs@cdrh.fda.gov.

Sincerely yours,

Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

Cc: [redacted] (purged copy)

[redacted] (purged copy)